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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,315	BLECK ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12,14-18,20-26,28 and 30-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 12, 14-18, 20-26, 28, and 30-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 11, 13, 19, 27, 29, and 42 have been cancelled.

Claims 1-10, 12, 14-18, 20-26, 28, and 30-41 are pending and under examination.

Response to Arguments

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-10, 12, 14-18, 20-26, 28, and 30-41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 36-74 and 94-102 of copending Application No. 11/928,464, in view of Schroder et al. (Biotech. Bioeng., 1997, 53: 547-559, of record).

This is a provisional obviousness-type double patenting rejection.

The instant claims are drawn to a method for transducing host cells by providing an immortal host cell and a plurality of retroviral vectors encoding a gene of interest, contacting the host cell at a multiplicity of infection from about 10 to 1000, repeating the above steps a plurality of time, clonally selecting the host cell expressing the gene of interest, and purifying the protein of interest (claims 1-10, 25, 28, 30, and 31). The retroviral vector is pseudotyped and comprises MoMLV elements, an exogenous promoter, a signal sequence, and an amplifiable marker such as DHFR (claims 12, 14-18, 20, 35, and 36) and the vector encodes at least two proteins, such as immunoglobulin heavy and light chains, arranged in a polycistronic sequence (i.e., the retroviral vector comprises IRES) (claims 22-24 and 39). Clonally selected cells are cultured in the presence of a selection agent such as methotrexate and could express 1, 10, or 50 pg per cell per day of the protein of interest (claims 32-34, 37, and 38), and the host cell comprises from 20 to about 100 integrated retroviral vectors (claim 41). The host cell can be a CHO or a 293 cell (claim 26) and the host cell can be transduced with at least two different vectors encoding different genes of interest (claim 40).

The application claims recite a method of transfecting a host cell and producing a protein of interest by providing a host cell and retroviral vectors comprising an exogenous promoter, a gene encoding for a protein of interest, contacting the host cell with the retroviral vector at a multiplicity of infection of 1000, and culturing the

transduced host cell such that the protein encoded by the gene of interest is produced, wherein between 2 and 1000 copies of retroviral vector integrate into the host cell genome; the host cell could be clonally selected and the protein of interest is further isolated (claims 36-43, 49, 51, 54, 56, 58-67, 69, 71-74, and 94-101). The retroviral vector is pseudotyped and comprises MoMLV elements, a signal sequence, an RNA stabilizing element IRES, at least two gene of interest such as the immunoglobulin genes arranged in a polycistronic sequence, the host cell is a CHO cell (i.e., immortal cell), the host cell secretes 1, 10, or 50 pg per cell per day of the protein of interest, and the host cell could comprise a second retroviral vector encoding a second protein of interest (claims 36-38, claims 44-48, 50, 52, 53, 55, 57, 68, 70, and 102). The application claims do not recite DHFR and methotrexate. Schroder et al. teach the amplification of hATIII expression in CHO cells via DHFR-mediated gene amplification in the presence of methotrexate (Abstract, Introduction, Table I). It would have been obvious to one of skill in the art, at the time the invention was made, to include an amplifiable marker, such as DHFR, into the instant vector and select with methotrexate for increased protein production, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Schroder et al. teach that increase synthesis of recombinant proteins in animal cells is commonly achieved by using gene amplification. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such a composition can be successfully made and used.

Thus, at the time of the invention, one of skill in the art would have considered the instantly pending claims an obvious variation of the application claims when viewed in light of the teachings of Schroder et al.

The applicant submits that he will file a terminal disclaimer when the other issues are resolved. The applicant's comments are acknowledged, however the rejection will be maintained until a terminal disclaimer is filed or claims are amended to obviate the rejection.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-10, 12, 14-18, 20, 21, 28, 30-34, and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. (Proc. Natl. Acad. Sci. USA,1996, 93: 10371-10376), in view of each Burns et al. (Proc. Natl. Acad. Sci. USA, 1993, 90: 8033-8037), Felts et al. (Strategies,1999, 12: 74-77), Schott et al. (Somatic Cells and molecular Genetics, 1996, 22: 291-309), and Persons et al. (Blood Cells, Molecules, and Diseases, 1998, 24: 167-182).

Mathor et al. teach a retroviral vector encoding human interleukin 6 (hIL-6), wherein the retroviral vector contains MoMLV LTRs, wherein the vector is used to

transduce keratinocytes at a MOI of 30, wherein the keratinocytes integrate multiple proviral copies in their genome, and wherein the transduced keratinocytes secrete hIL-6 at a rate of approximately 800 ng per 10^6 cells per day during their lifetime (i.e., the cells secrete more than 1 pg per cell per day); the transduced cells are grown as mass cultures or are cloned by limiting dilution (claims 1, 18, 20, 28, 31, 32) (Abstract, p. 10371, column 2, second paragraph, Material and Methods, p. 10372, columns 1 and 2, p. 10373, column 2). Since hIL-6 is secreted, the retroviral vector must necessarily comprise a segment encoding a secretion signal sequence operably linked to the gene encoding for hIL-6 (claim 21). Mathor et al. teach clonal analysis by Southern blot and by radioimmunoassay, wherein the radioimmunoassay is performed on isolated hIL-6 (claims 1 and 30) (p. 10372, columns 1 and 2, p. 10374, p. 13075, column 1 and Fig. 4, p. 10636, column 1). Mathor et al. teach 11 clones with 1 to 15 proviral integrations, i.e., Mathor et al. teach clonally selecting at least 1 or 10 colonies (claims 35 and 36) (p. 10373, Table 1). Mathor et al. also teach that the retroviral vector is produced from packaging cell lines transfected with an envelope plasmid and a vector plasmid, wherein the packaging cell line expresses gag and pol proteins (claims 12 and 14) (p. 10371, column 2 bridging p. 10372).

Mathor et al. do not teach immortal cells (claim 1), nor do they teach 293-GP cells (claim 15), or VSV-G protein (claims 16 and 17). Burns et al. teach producing retroviral vectors pseudotyped with VSV-G, wherein the vectors are produced in 293-G cells and wherein the pseudotyped retroviral vectors are able to mediate stable gene transfer in cell lines such as the BHK cell line (i.e., immortal cells) (Abstract, p. 8033,

columns 1 and 2, p. 8035, column 1, second paragraph). Based on these teachings, one of skill in the art would have known that immortal cells could also be used in the method of Mathor et al. and would be motivated to modify the method of Mathor et al. by substituting their secondary cells with immortal cells to achieve the predictable result of obtaining consistent production of desired proteins for unlimited time. Furthermore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. by using the pseudotyped retrovirus of Burns et al., with a reasonable expectation of success. The motivation to do so is provided by Burns et al., who teach that such a virus has an expanded host range (Abstract, p. 8033, column 2). One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such a composition can be successfully made and used.

Mathor et al. and Burns et al. do not specifically teach serial transduction to a obtain cell comprising in its genome from 20 to about 100 integrated vectors (claims 1-10 and 41). However, Mathor et al. do teach that protein expression is directly proportional to the integration events (i.e., copy number) (p. 10376, column 1). Additionally, the prior art as a whole teaches that there is a positive correlation between the MOI and integration events. For example, Felts et al. teach that the advantage of retroviral vectors is that the copy number of integrated provirus can easily be controlled by varying the multiplicity of infection (MOI) (p. 74). Schott et al. teach serially transducing cells with a retroviral vector carrying an internal promoter driving the expression of a gene of interest, wherein higher MOI result in higher integration events

and wherein the expression and stability of the gene of interest directly correlates with the number of integrated retroviral vectors (Abstract, p. 292, column 2, p. 294, column 2, second paragraph, p. 295, column 1, p. 302, column 2, first full paragraph, p. 303, column 2 and Fig. 9, p. 308, column 1). Persons et al. teach that repeatedly transducing cells with retroviral vectors at a MOI of 1,000 results in cells comprising 20 copies of integrated retroviral vector (Abstract, paragraph bridging p. 168 and 169, p. 171, column 2, last paragraph, p. 172, column 2, last paragraph, p. 173, column 2, p. 174, column 2, p. 177, column 2, p. 179, column 1, first full paragraph). Based on these teachings, one of skill in the art would have known that serially transducing cells with high MOI would result in increased proviral integration events. It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. and Burns et al. by serially transducing their cells with high MOIs (such as MOIs of 1,000) to achieve the claimed ranges of integration events, with a reasonable expectation of success. The motivation to do so is provided by Mathor et al., who teach the possibility of specifying the level of transgene expression by controlling the integration events (Abstract, p. 10376, column 1). One of ordinary skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that the level of retroviral vector integration events can be easily controlled by manipulating the MOI. With respect to the limitation of an internal promoter (claim 1), using such was routine in the prior art, as taught by Schott et al. (p. 292, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. and Burns et al. by further

including an internal promoter in their vector to achieve the predictable result of expressing hIL-6 in their cells. With respect to the limitations of one cell secreting more than 10 or 50 pg protein per day (claims 33 and 34), one of skill in the art would have had known to obtain the desired amounts of synthesized proteins by controlling the number of integration events.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

6. Claims 1-10, 12, 14-18, 20, 21, 26, 28, 30-38, and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with each Burns et al., Felts et al., Schott et al., and Persons et al., in further view of Schroder et al. (Biotech. Bioeng., 1997, 53: 547-559).

The teachings of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. are applied as above for claims 1-10, 12, 14-18, 20, 21, 28, 30-34, and 41. Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. do not teach DHFR and culturing the transduced cells in the presence of methotrexate (claims 35-38), nor do they teach Chinese hamster ovary (CHO) cells (claim 26). Schroder et al. teach the amplification of hATIII expression in CHO cells via DHFR-mediated gene amplification in the presence of methotrexate (Abstract, Introduction, Table I). It would have been obvious to one of skill in the art, at the time the invention was made, to include an amplifiable marker, such as DHFR, into the vector of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. for increasing protein production and to

use the modified vector for the transduction of CHO cells, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Schroder et al. teach that increase synthesis of recombinant proteins in animal cells is commonly achieved by using gene amplification. One of skill in the art would have been motivated to use CHO cells because they are known to be an excellent model cell line for the production of high levels of proteins of interest. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such a composition can be successfully made and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

7. Claims 1-10, 12, 14-18, 20-24, 26, 28, 30-34, and 39-41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with each Burns et al., Felts et al., Schott et al., and Persons et al., in further view of both Primus et al. (Cancer Res., 1997, 53: 3355-3361) and Kolb et al. (Hybridoma, 1997, 16: 421-426, Abstract).

The teachings of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. are applied as above for claims 1-10, 12, 14-18, 20, 21, 28, 30-34, and 41. Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. do not teach at least two different vectors encoding different genes of interest (claim 40). Primus et al. teach a method of expressing a monoclonal IgG2a antibody into a tumor cell, wherein the tumor cell is transduced with two different vectors, one encoding the heavy and the other encoding the light chain (claim 40), and wherein the transduced tumor cell

produces self-reactive antibodies (Abstract, p. 3355, column 1, p. 3356, column 1, first full paragraph, p. 3360, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. to express antibodies into a cancer cell, as taught by Primus et al., with a reasonable expectation of success. The motivation to do so is provided by Primus et al., who teach that antibody gene transfer into autologous tumor cells offer a new and alternative application in the use of antibodies for the immune therapy of cancer. One of skill in the art would have been expected to have a reasonable expectation of success in making such a composition because the art teaches that such a composition can be successfully obtained.

Mathor et al., Burns et al., Felts et al., Schott et al., Persons et al., and Primus et al. do not teach the two genes of interest being arranged in a polycistronic sequence, wherein the genes of interest are the immunoglobulin heavy and light chains (claims 22-24 and 39). Kolb et al. teach concurrent synthesis of both heavy and light chains of the monoclonal antibody A1 by using a bicistronic expression cassette comprising an internal ribosomal entry site (IRES) (Abstract). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al., Burns et al., Felts et al., Schott et al., Persons et al., and Primus et al. by using the expression cassette of Kolb et al. for the production of monoclonal antibodies of interest, with a reasonable expectation of success. The motivation to do so is provided by Kolb et al., who teach that their method allows for the rapid isolation of cell clones expressing high levels of recombinant antibody. One of skill in the art would have been

expected to have a reasonable expectation of success in making such a composition because the art teaches that such a composition can be successfully obtained.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

8. Claims 1-10, 12, 14-18, 20, 21, 25, 28, 30-34, and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with each Burns et al., Felts et al., Schott et al., and Persons et al., in further view of Naldini et al. (Science, 1996, 272: 263-267).

The teachings of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. are applied as above for claims 1-10, 12, 14-18, 20, 21, 28, 30-34, and 41. Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. do not teach a lentiviral vector (claim 25). Naldini et al. teach lentiviral vector for the stable transduction of non-dividing cells (Abstract, p. 263, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. by using the lentiviral vector of Naldini et al., with a reasonable expectation of success. The motivation to do so is provided by Naldini et al., who teach that their vector can be used for the transduction of non-proliferating cells such as hepatocytes, myofibers, hematopoietic stem cells, and neurons. One of skill in the art would have been expected to have a reasonable expectation of success in using such a composition because the art teaches that such a composition can be successfully used.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Most of the arguments are not new and were previously addressed.

The applicant argues that any attempt to correlate the data from Mathor et al. to the claimed range of 20-100 integrations is speculation without factual basis because the data Mathor et al. is not amenable for statistical analysis. This is not found persuasive for the reasons set forth in the prior Office actions. Furthermore, one of skill in the art would not need a statistical analysis in Mathor et al. The prior art teaches that retroviral insertion into the genome is random and that expression level is dependent on the insertion site. Thus, one of skill in the art would have known that it is statistically probable to obtain clones which, albeit having the same number of retroviral copies inserted into their chromosomes, express different amounts of retroviral-encoded proteins. This is evidenced by the data presented by Mathor et al. in Table 1. One of skill in the art would have reasonably expected to obtain high secreting clones by increasing the copy number. Please also note that Persons et al. teach stable host cells comprising 20 copies of integrated retroviral vector, wherein the host cells are very efficient in generating high titers of retroviral vector.

The applicant argues that Persons et al. is directed to packaging cell lines for the production of infectious virus and thus, their teachings are not relevant to cells transduced to make proteins of interest. This is not found persuasive. Persons et al.

teach host cells comprising 20 copies of integrated retroviral vector, wherein the host cells are very efficient in generating high amounts of retroviral vector, i.e., the inserted retroviral vector is efficiently expressed. Thus, Persons et al. provide evidence that achieving 20 integrated copies is feasible and useful to obtain high expression levels and this is relevant for the expression of any transgene. Apart from an argument, the applicant did not provide any evidence to the contrary.

The applicant argues that Schott et al. only teaches a correlation over a range of 1-9 integrations. This is not found persuasive because Schott et al. do not have to teach each and every claim limitation. Obtaining stable host cells comprising 20 copies of integrated retroviral vector is taught by Persons et al.

The applicant argues that the state of the prior art was that the retroviral vectors are inactivated by methylation and that the inactivation by methylation is exacerbated by increasing the copy numbers. The applicant argues that the Fifth Bleck Declaration filed on 10/07/2010 establishes that the cells inactivate transcription and thus reduce expression from retroviral vectors.

This is not found persuasive. Although the references provided with the Fifth Bleck Declaration disclose that transgene can be transcriptionally inactivated by methylation, none provides any evidence that one of skill in the art would not have been able to obtain clones comprising multiple integrated copies of integrated viral vectors and use these clones to produce proteins of interest. According to the applicant, the

references provided with the Fifth Bleck Declaration teach away from obtaining cells with multiple copies of integrated retroviral vectors. This is not found persuasive. Please note that the teachings of the provided references apply to any number of integrated vectors, including one integrated copy. None of the references sets a limit beyond which gene expression is inactivated by methylation. None of the references indicate that transcriptional inactivation by methylation in cells *in vitro* takes place by increasing the copy number beyond 15. Thus, none of the references provide a basis for applicant's assertion that one of skill in the art would not have been motivated to increase the copy number beyond 15. Importantly, Mathor et al. art teach efficiently expressing proteins of interest by using host cells comprising 15 copies of integrated retroviral vectors and Persons et al. teach host cells comprising 20 copies of integrated retroviral vector, wherein the host cells are very efficient in generating high titers of retroviral vector (i.e., the integrated copies are not silenced by methylation) (Abstract; paragraph bridging p. 168 and 169; p. 172, column 2, last paragraph, p. 173, column 2, p. 174, column 2, p. 177, column 2, p. 179, column 1, first full paragraph). This is evidence that the teachings of the references provided by the applicant did not impede one of skill in the art to obtain and successfully use host cells with 15 and more copies of integrated retroviral vectors. Furthermore, there is no basis for the assertion that inactivation by methylation is exacerbated by increasing the copy numbers. To support this assertion, the applicant cites Mehtali et al. (Gene, 1990, 91: 179-184). The teachings of Mehtali et al. are related to transgene methylation in transgenic mice *in vivo*. Although they teach that methylation increases with increasing the copy number,

Mehtali et al. do not teach that this necessarily results in decreased transgene expression. Specifically, Table I indicates that transgene expression increases with increasing the copy number from 10 to 22. Table I also demonstrates that the same copy number results in different levels of expression in different transgenic animals, which is consistent with the teachings in the art that insertion is random and that expression level is dependent on the insertion site. Based on the teachings in the art as a whole, one of skill in the art would reasonably expect that increasing the copy number beyond 15 would result in increased protein production; one of skill in the art would also know that clones with the same number of copies could have different expression levels, and therefore, would know to select multiple clones and look for the high expressing ones. Please note that the claimed invention is subjected to the same variability (see Examples on p. 91-93 and 104). The specification does not provide more than that which was known in the prior art.

The applicant argues that, since Gunzburg et al. relate to endogenous and not exogenous proviral sequences and since they do not show data nor do they provide comments addressing any correlation of methylation and gene expression, their teachings have very little relevance to the instant invention. The applicant also argues that neither Stamps et al. nor Liu et al. teach a correlation between copy number and transgene expression. These arguments are not material to the instant rejection because the references were no used to reject the claims and because the references were not cited for providing data correlation copy number with transgene expression.

The references were only cited as evidence that the existence of a correlation between the insertion site and transgene expression level was common knowledge in the prior art. Furthermore, Gunzburg et al. do teach that there is a correlation between the insertion site and expression of retroviral genes for both endogenous and exogenous proviral sequences, including MoMLV (p. 1129, bridging columns 1 and 2; paragraph bridging p. 1133 and 1134; p. 1134, column 1). Thus, the teachings of Gunzburg et al. are relevant to the instant invention.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633